



(19)

Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 0 741 188 A3

(12)

EUROPEAN PATENT APPLICATION

(88) Date of publication A3:
14.07.1999 Bulletin 1999/28

(43) Date of publication A2:
06.11.1996 Bulletin 1996/45

(21) Application number: 96303133.1

(22) Date of filing: 03.05.1996

(51) Int. Cl.⁶: C12N 15/17, C12N 5/10,
C07K 14/62, A61K 38/28,
A61K 48/00

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL
PT SE
Designated Extension States:
AL LT LV SI

(30) Priority: 05.05.1995 US 435762
05.05.1995 US 435503

(71) Applicant: ELI LILLY AND COMPANY
Indianapolis, Indiana 46285 (US)

(72) Inventors:
• Chance, Ronald Eugene
Westfield, Indiana 46074 (US)

- Dimarchi, Richard Dennis
Carmel, Indiana 46033 (US)
- Hoffmann, James Arthur
Greenwood, Indiana 46143 (US)
- Long, Harlan Beall
Carmel, Indiana 46032 (US)
- Miller, Anne Reifel
Indianapolis, Indiana 46208 (US)

(74) Representative:
Hudson, Christopher Mark et al
Lilly Industries Limited
European Patent Operations
Erl Wood Manor
Windlesham Surrey GU20 6PH (GB)

(54) Single chain insulin with high bioactivity

(57) The instant invention provides polypeptide compounds of the formula b-BP-a having significant insulin activity, nucleotide sequences encoding said polypeptides, vectors comprising said nucleotide sequences, and cell lines transformed with said vectors useful for treating diabetes.

BEST AVAILABLE COPY

EP 0 741 188 A3



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 30 3133

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
P,X	WO 95 16708 A (NOVO NORDISK A/S (DK); KRISTENSEN C.; KJELDSEN T.; ANDERSEN A.) 22 June 1995 * the whole document *	1-4,6-8, 10,11	C12N15/17 C12N5/10 C07K14/62 A61K38/28 A61K48/00
E	US 5 840 542 A (MOGAN BIOTECHNOLOGY RESEARCH INSTITUTE (KR); KANG YUP; YOON JI-WON) 24 November 1998 * table 1 *	1-3,5-11	
X	EP 0 068 701 A (CANADIAN PATENTS AND DEVELOPMENT LIMITED (CA); NARANG S.A.; WU R.J.) 5 January 1983 * page 5 *	1-3,5-11	
Y	* page 13 - page 16 *	12	
Y	* page 19 - page 20; claims *		
Y	STEWART C. ET AL.: "Insulin delivery by somatic cell gene therapy" JOURNAL OF MOLECULAR ENDOCRINOLOGY, vol. 11, 1993, pages 335-341, XP002912202 * abstract *	12	
X	EP 0 195 691 A (NOVO INDUSTRI A/S (DK); THIM L.; NORRIS K.; HANSEN M.T.) 24 September 1986 * page 13; table 1 *	1-3,6-8, 10,11	C12N C07K A61K
X	THIM L. ET AL.: "Secretion and processing of insulin precursors in yeast" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol. 83, no. 18, September 1986, pages 6766-6770, XP002100937 * page 6768; table 1 *	1-3,6-8, 10,11	
-/--			
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 27 April 1999	Examiner Macchia, G
CATEGORY OF CITED DOCUMENTS X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document		T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons &: member of the same patent family, corresponding document	

EPO FORM 1503 03.82 (P04C01)



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 30 3133

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP 0 163 529 A (NOVO INDUSTRI A/S (DK); MARKUSSEN FIIL AMMERER HANSEN THIM NORRIS VOIGT) 4 December 1985 * abstract * * page 10 * * page 13; table 1 * * page 32 - page 35; claims * ---	1-3,6-8, 10,11	
X	EP 0 427 296 A (NOVO NORDISK A/S (DK); MARKUSSEN FIIL AMMERER HANSEN THIM NORRIS VOIGT) 15 May 1991 * abstract * * page 7; table 1 * ---	1-3,6-8, 10,11	
P,X	EP 0 678 522 A (ELI LILLY CO (US); CHANCE R.E.; DIMARCHI R.D.; FRANK B.H.; SHIELDS J.E.) 25 October 1995 * abstract * * page 5 - page 6 * ---	1-3,6-8, 10,11	
E	GB 2 298 206 A (HANIL SYNTHETIC FIBER CO LTD (KR)) 28 August 1996 * abstract * ---	1,2,6-8, 10,11	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A	NEWGARD C.B.: "Cellular engineering and gene therapy strategies for insulin replacement in diabetes" DIABETES, vol. 43, no. 3, 1 March 1994, pages 341-350, XP000571434 * the whole document * -----	12	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 27 April 1999	Examiner Macchia, G
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document</p>			

EPO FORM 1503 03.92 (P04C01)



European Patent
Office

Application Number
EP 96 30 3133

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☒ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- ☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:



European Patent
Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 96 30 3133

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 4 totally; 1-3, 6-8, 10-12 all partially

A polypeptide compound of the formula b-BP-a, wherein b and a are the B and A chains of insulin, respectively, and BP is a bridging peptide, namely as in Seq.ID:2 and 4.
Pharmaceutical formulation comprising said polypeptide.
Nucleotide sequence encoding said polypeptide, vector comprising said nucleotide sequence, cell line transformed with said vector.

2. Claims: 5, 9 totally; 1-3, 6-8, 10-12 all partially

As invention 1 but concerning Seq.ID:1,3,5

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 96 30 3133

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-04-1999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9516708 A	22-06-1995	AU 1272295 A	03-07-1995
US 5840542 A	24-11-1998	NONE	
EP 0068701 A	05-01-1983	CA 1204682 A	20-05-1986
		JP 58004800 A	11-01-1983
		US 4792602 A	20-12-1988
EP 0195691 A	24-09-1986	DK 129385 A	23-09-1986
		AT 69266 T	15-11-1991
		AU 586855 B	27-07-1989
		AU 5500586 A	25-09-1986
		DE 3682303 A	12-12-1991
		DK 125786 A,B,	17-11-1986
		FI 861198 A,B,	23-09-1986
		GR 860764 A	21-07-1986
		IE 58842 B	17-11-1993
		JP 1923989 C	25-04-1995
		JP 6048993 B	29-06-1994
		JP 61221200 A	01-10-1986
		JP 2092913 C	18-09-1996
		JP 6133777 A	17-05-1994
		JP 8008871 B	31-01-1996
		JP 2553326 B	13-11-1996
		JP 8023985 A	30-01-1996
		PT 82241 A,B	01-04-1986
EP 0163529 A	04-12-1985	AT 66490 T	15-09-1991
		AT 143374 T	15-10-1996
		AU 590197 B	02-11-1989
		AU 4309285 A	05-12-1985
		CA 1304022 A	23-06-1992
		DE 3583824 A	26-09-1991
		DE 3588125 D	31-10-1996
		DK 238585 A,B,	01-12-1985
		DK 323687 A,B,	25-06-1987
		EP 0427296 A	15-05-1991
		FI 852135 A,B,	01-12-1985
		GR 851304 A	25-11-1985
		IE 66387 B	27-12-1995
		IE 80630 B	21-10-1998
		JP 1907704 C	24-02-1995
		JP 6030613 B	27-04-1994
		JP 61001389 A	07-01-1986
		JP 2084771 C	23-08-1996
		JP 6141866 A	24-05-1994

EPO FORM P0458

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 96 39 3133

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-04-1999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0163529 A		JP 7121226 B	25-12-1995
		JP 2011125 C	02-02-1996
		JP 6141865 A	24-05-1994
		JP 7046998 B	24-05-1995
		JP 2519023 B	31-07-1996
		JP 7309896 A	28-11-1995
		NO 174351 B	10-01-1994
		PT 80551 A,B	01-06-1985
		US 4916212 A	10-04-1990
EP 0427296 A	15-05-1991	AT 66490 T	15-09-1991
		AT 143374 T	15-10-1996
		AU 590197 B	02-11-1989
		AU 4309285 A	05-12-1985
		CA 1304022 A	23-06-1992
		DE 3583824 A	26-09-1991
		DE 3588125 D	31-10-1996
		DK 238585 A,B,	01-12-1985
		DK 323687 A,B,	25-06-1987
		EP 0163529 A	04-12-1985
		FI 852135 A,B,	01-12-1985
		GR 851304 A	25-11-1985
		IE 66387 B	27-12-1995
		IE 80630 B	21-10-1998
		JP 1907704 C	24-02-1995
		JP 6030613 B	27-04-1994
		JP 61001389 A	07-01-1986
		JP 2084771 C	23-08-1996
		JP 6141866 A	24-05-1994
		JP 7121226 B	25-12-1995
		JP 2011125 C	02-02-1996
		JP 6141865 A	24-05-1994
		JP 7046998 B	24-05-1995
		JP 2519023 B	31-07-1996
		JP 7309896 A	28-11-1995
		NO 174351 B	10-01-1994
		PT 80551 A,B	01-06-1985
		US 4916212 A	10-04-1990
EP 0678522 A	25-10-1995	AT 133961 T	15-02-1996
		AU 630912 B	12-11-1992
		AU 4922690 A	16-08-1990
		BG 60769 B	29-02-1996
		CA 2009579 A	09-08-1990
		CN 1044820 A,B	22-08-1990
		CN 1148984 A	07-05-1997

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 96 30 3133

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-04-1999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0678522 A		DE 69025210 D	21-03-1996
		DK 383472 T	06-05-1996
		EP 0383472 A	22-08-1990
		ES 2083424 T	16-04-1996
		FI 95915 B	29-12-1995
		GR 3019501 T	31-07-1996
		HK 60296 A	12-04-1996
		HU 212679 B	30-09-1996
		HU 9500171 A	28-08-1995
		IE 73251 B	21-05-1997
		IL 93282 A	31-08-1995
		JP 2110045 C	21-11-1996
		JP 2264798 A	29-10-1990
		JP 8022878 B	06-03-1996
		LU 88830 A	06-01-1997
		LU 88831 A	10-01-1997
		LV 10291 A,B	20-10-1994
		MX 19389 A	28-02-1994
		NO 179587 B	29-07-1996
		NO 950721 A	10-08-1990
		PT 93057 A,B	31-08-1990
		US 5514646 A	07-05-1996
		US 5700662 A	23-12-1997
GB 2298206 A	28-08-1996	KR 150565 B	17-08-1998
		DE 19605657 A	22-08-1996
		FR 2730495 A	14-08-1996
		JP 8333395 A	17-12-1996

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☒ **FADED TEXT OR DRAWING**
- ☒ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☒ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.